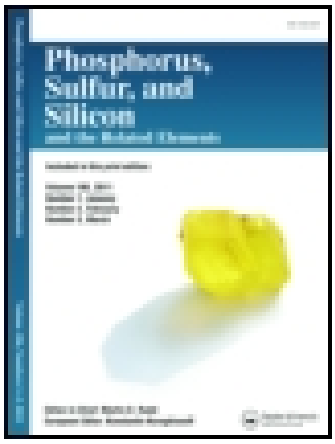

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AN UNUSUAL REACTION OF DIMETHYL AZODICARBOXYLATE WITH H-DIMETHYLPHOSPHONATE

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When the commonly used phosphorus components of the cocktail of the classical Mitsunobo reaction are changed from triphenylphosphine and trialkylphosphite to H-dimethylphosphonate, the course of the reaction changes and leads to products arising from the involvement of the free radical reaction. This article presents the mass spectral characterization of the novel compounds along with the probable mechanism of their formation.

Keywords: —CI characterization; diethyl azodicarboxylate; free radical participation; GC-MS-EI; H-dimethylphosphonate; Mitsunobu reaction; novel compounds

Hydrogen mono- and diphosphonates (H-phosphonates) have found particular application in phosphorylation reactions and in the synthesis of oligonucleotides.[1] The hydrogen directly attached to the phosphorus atom is readily abstractable.[1c] Also, H-phosphonates are known to add to carbon-carbon double bonds.[2a,b] Recently we reported that H-phosphonate adds to the carbon-carbon double bond of perfluoromonoalkenes to give various products.[3] The H-phosphonates also attack the carbonyl group.[4] Free radical catalyzed reaction of H-phosphonate with styrene oxide has recently been published.[5] Air oxidation of trialkylphosphines and trialkylphosphites has been described to yield products including phosphates via the free radical process.[6] During the free radical reaction and the exposure to microwaves,

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H-dimethylphosphonate (**1**) was transformed into trimethyl-phosphate and tetramethylpyrophosphate.[3]

Diethyl azodicarboxylate (DEAD, **2**) and triphenylphosphine or trialkyl-phosphites form the necessary constituents of the cocktail used in the classical Mitsunobu reaction. The versatility and wide applicability of the Mitsunobu reaction in constructing carbon-carbon bond have been described in detail.[7] The reaction of PPh_3 and DEAD has been stated to form N-alkyl-N′-bis-(alkoxy)phosphoryl-hydrazine-carboxylate via the phosphonium salt intermediate.[8a] Although this suggestion has been questioned,[8b] the formation of the phosphonium salt intermediate during the Mitsunobu reaction has been well documented.[8c] In fact, a stable oxy phosphonium salt has been isolated and identified.[8d] Several studies of the mechanism of the Mitsunobu reaction have appeared.[9] The formation of the adduct appears to occur within seconds.[9a] It has been suggested that the reaction follows a dual mechanism in the presence of CF_3CO_2H.[9c]

The DEAD-PPh_3 adduct has been stated to cause dehydrative decarboxylation of β-hydroxy carboxylic acids to yield cis and trans olefinic products.[10a] The combination of DEAD-PPh_3 can be conveniently used, instead of dicyclohexylcarbodiimide, in the preparation of esters from acids and alcohols.[10b] Secondary hydroxyl group can be transformed into amino group by reacting it with phthalimide under the conditions of the Mitsunobu reaction followed by reduction.[10c] Also, the secondary alcoholic group can be replaced with N_3 by conducting the Mitsunobu reaction in the presence of HN_3.[10d,e] Interestingly, DEAD also reacts with the carbon-carbon double bond.[11] Alkylation of active methylene compounds under the Mitsunobu conditions yields both mono- and dialkylated products accompanied by diethyl N-alkylated hydrazinedicarboxylate.[12a] The reaction also has found application in the preparation of β-lactams.[12b,c] A novel application of DEAD is its use in the steroespecific synthesis of aminated products, in particular biologically active and useful amino acids.[13] Propargyl alcohols have been transformed into allenes.[11d]

In continuation of our interest in the chemistry of H-dimethylphosphonate (**1**),[3,5,14] its reaction with DEAD (**2**) has now been investigated. Among the novel compounds identified are products derived from the free radical reaction of H-dimethylphsphonate (**1**) with DEAD and toluene, the latter being the solvent. The GC-MS characterization of various compounds [**3**∼**14**, cf. Figure 1] and the probable mechanism of formation of the unusual compounds are presented in this article.

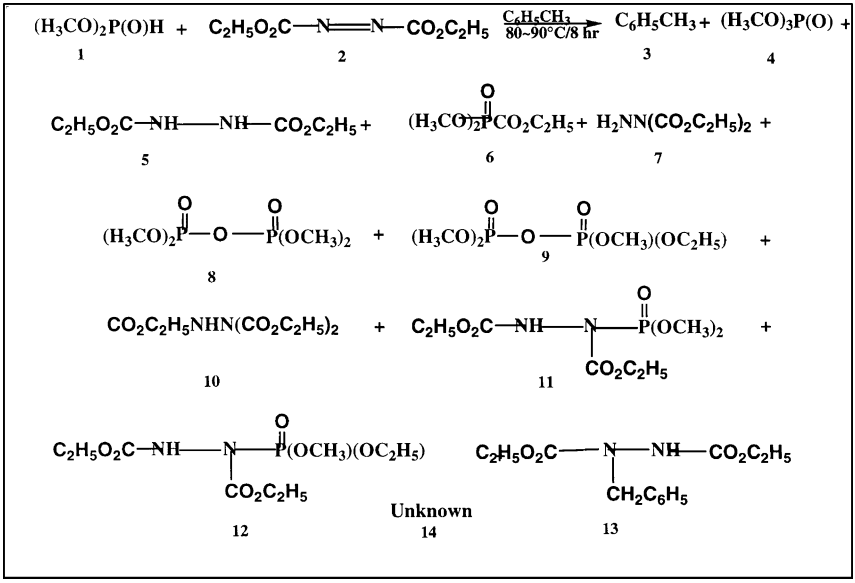

FIGURE 1 Structures of compounds cited in the text.

RESULTS AND DISCUSSION

In the light of the reported addition of H-dimethylphosphonate (**1**) to carbon-carbon double bond of α-nitrostyrene,[15] the first reaction we explored was its reaction with cinnamonitrile. Both microwave cooking of a mixture of cinnamyl nitrile and H-dimethylphosphonate (**1**) in the presence of activated molecular sieve powder for 10 min and refluxing a solution of the two in toluene overnight gave only the starting material. The GC of the reaction product failed to detect the presence of any other compounds. Since we recently had observed the addition of difluorocarbene across the nitrogen-nitrogen double bond of DEAD,[16] it was interesting to see whether H-dimethylphosphonate (**1**) would react with DEAD (**2**). Accordingly, a solution of DEAD (**2**) and H-dimethylphosphonate (**1**) in toluene was heated for 8 h at 80∼90°C (oil bath temperature) under nitrogen and with stirring. The GC analysis of the reaction product showed it to be a complex mixture of compounds. The GC-MS analysis of the product after the removal of the solvent under reduced pressure showed it to consists of 12 components. A careful study of the mass spectral fragmentation behavior enabled

the characterization of all but one component. The unknown compound (**14**) failed to give its molecular ion peak. It underwent extensive fragmentation in the mass spectrometer before its molecular weight was recorded. In view of the unusual nature of the structures of some of the compounds, the sample was reexamined using both EI and CI modes to confirm the molecular weights of all compounds. Even under the GC-MS CI mode, the unknown compound (**14**) was observed to undergo extensive fragmentation. The GC-MS-CI enabled us to confirm the molecular ion peaks of all of the compounds except **14** (cf. Table I).

Toluene and trimethylphosphate (**4**) are the first to come off (Figure 1). The mass spectrum of **4** already has been recorded.[3,5] Diethyl hydrazinedicarboxylate (**5**), carbethoxydimethylphosphonate (**6**), and 1,1-diethylhydrazinedi-carboxylate (**7**) are the next to come off the GC-MS column. There is nothing unusual about compound **5**.[9d]

TABLE I Mass Spectral Fragmentation of the Compounds Cited in the Text[a]

5. Compound 5: $M^+ = 176$ (r.t. = 5.55 min; 2.0%); 130 (M—CO_2-2H); 103 (M—$CO_2C_2H_5$); 91 (M—CH_3—$CO_2C_2H_5$); 87 ($NCO_2C_2H_5$); 84 ($C_4H_8N_2$); 73 ($CO_2C_2H_5$, 100%); 59 ($C_2H_7N_2$); 57 ($C_2H_5N_2$) and 45 (C_2H_7N or OC_2H_5).
6. Compound 6: $M^+ = 182$ (r.t. = 6.03 min; 0.6%); 153 (M—C_2H_5); 139 (153-CH_2); 109 (M—$CO_2C_2H_5$, 100%); 95 [(HO)P(O)(OCH_3)]; 79 [PH(O)(OCH_3)]; 65 (PH_2O_2); and 47 (PO).
7. Compound 7: $M^+ = 176$ (r.t. = 7.52 min; 6.0%); 148 (M—C_2H_4); 130 (M-$_2$H—CO_2); 117 (M—CO_2—NH); 104 (148-CO_2, 100%); 89 (104-CH_3); 76 (C_4H9N_2); 59 ($C_2H_7N_2$) and 45 (C_2H_7N or OC_2H_5).
8. Compound 9: $M^+ = 248$ (r.t. = 8.18 min; 0.2%); 221 (M—C_2H_3, 100%); 203 (M—OC_2H_5); 190 (221—OCH_3); 171 (203-OCH_2); 159 (191-CH_3OH); 145 (159-CH_2); 127 [$(CH_3O)_2P(OH)_2$]; 109 [$(CH_3O)_2P(O)$]; 95 [(HO)P(O)(OCH_3)]; 81 (H_2PO_3); 79 (PO_3); 65 (PH_2O_2); 63 (PO_3) and 47 (PO).
10. Compound 10: $M^+ = 248$ (r.t. = 10.05 min; 7.5%); 203 (M—OC_2H_5); 176 (M—$CO_2C_2H_4$, 100%); 158 (M—CO_2H or —OC_2H_5); 130 ($H_5C_2NNCO_2C_2H_5$); 104 (176-$C_3H_4O_2$); 89 ($C_3H_7NO_2$); 75 ($C_2H_7N_2O$); 59 ($C_2H_7N_2$) and 45 (OC_2H_5).
11. Compound 11: $M^+ = 284$ (r.t. = 11.14 min; 66.9%); 239 (M—CO_2H); 212 (M—$CO_2C_2H_4$); 194 (239-OC_2H_5); 166 [$H_5C_2N_2P(O)(OCH_3)_2$]; 158 ($C_6H_{10}N_2O_3$); 155 [$CH_3N_2H_3P(O)(OCH_3)_2$]; 140 [$N_2H_3P(O)(OCH_3)_2$ or 155-CH_3]; 127 [$P(HO)_2(OCH_3)_2$, 100%]; 110 [$PH(O)(OCH_3)_2$]; 109 [$P(O)(OCH_3)_2$]; 93 [$CH_3P(O)(OCH_3)_2$]; 65 [$P(OH)_2$] and 47 (PO).
12. Compound 12: $M^+ = 298$ (r.t. = 11.42 min; 2.1%); 253 (M—OC_2H_5 or CO_2H); 226 (M—$CO_2C_2H_4$); 180 (180-C_2H_4); 169 (198-C_2H_4); 158 $C_6H_{10}N_2O_3$), 153 ($C_3H_{11}N_2O_3P$); 126 ($C_3H_{11}NO_3P$, 100%); 95 (CH_4O_3P); 81 (H_2PO_3); 79 (PO_3); 65 (H_2PO_2); 57 (C_2H7N_2) and 47 (PO).
13. Compound 13: $M^+ = 266$ (r.t. = 11.98 min; 8.5%); 193 (M—$CO_2C_2H_5$); 178 ($C_6H_5CH_2NCO_2C_2H_5$); 150 (178-C_2H_4); 133 (178-OC_2H_5); 121 (193—$CO_2C_2H_4$); 106 ($C_6H_5CH_2NH$); 91 ($C_6H_5CH_2$, 100%); 77 (C_6H_5) and 51 (C_4H_3).
14. Compound 14: M^+ = Not Seen (r.t. = 12.9 min; 0.2%).

[a]Mass spectra were run both in EI and CI modes.

Compound **5** and its derivatives are frequently encountered in working with DEAD.[9c] However, the formation of compounds **6** and **7** needs some explanation (cf. Figure 2).

There are not many examples of the free radical reactions of DEAD (**2**). It has been stated that cyclic monoalkenes react with DEAD (**2**) via

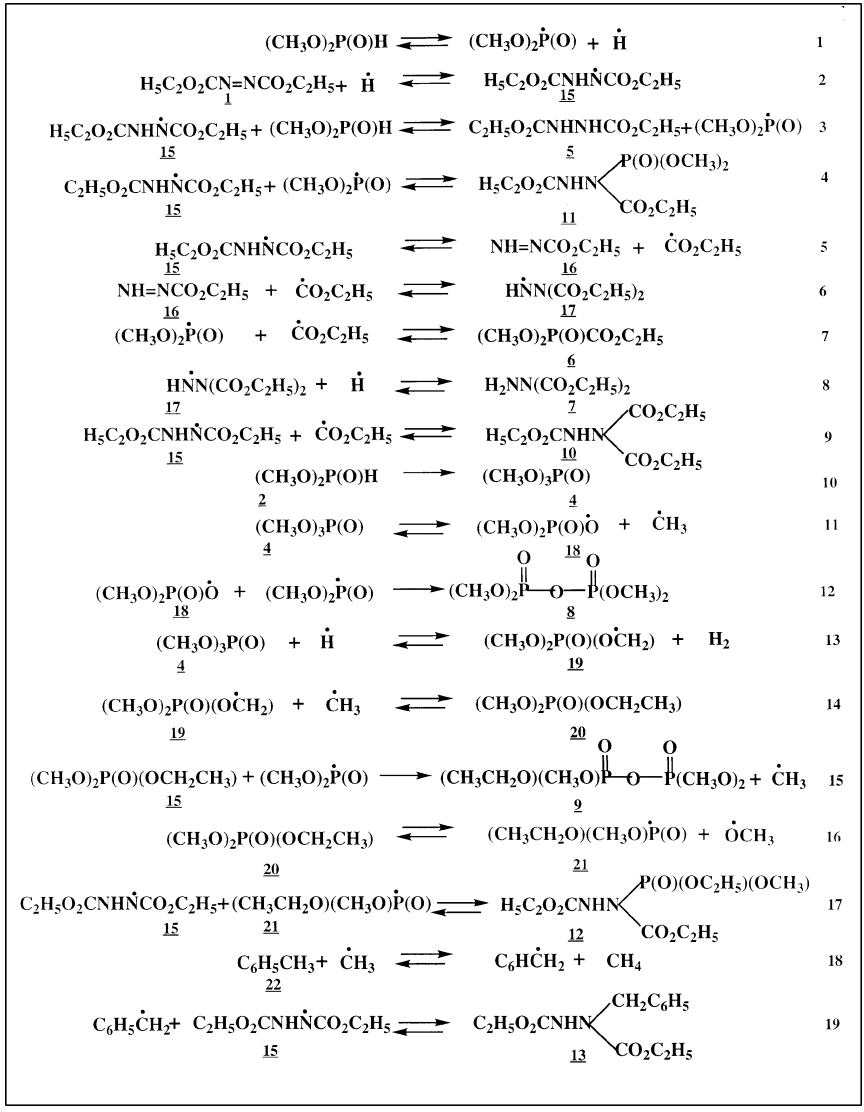

FIGURE 2 Probable mechanism of formation of compounds cited in the text.

a free radical process, while the acyclic monoalkenes do not.[11] Allylic radicals are said to add across the nitrogen-nitrogen double bond of DEAD to initially give the "bicarbamyl radical," which then is described to abstract hydrogen from the olefin.[11b]

The formation of **6** and **7** can be rationalized as shown in Figure 2. The hydrazinyl radical (**15**) formed by the addition of hydrogen spilt off from H-dimethylphsophonate (**1**) (cf., Figure 2) can then abstract hydrogen from **1** to form the product, namely **5** and the phosphoryl radical. Functionalized diazenes have been reported to form radical species photolytically and thermally.[17] Else, the hydrazinyl radical (**15**) can split off the carbethoxy radical to give ethyl diazocarboxylate (**16**). The carbethoxy radical thus split off from **15** can then go on to add to the hydrazinyl radical (**15**) to furnish triethyl hydrazenecarboxylate radical (**10**). The same carbethoxy radical also can add to the dimethylphosphoryl radical to yield carbethoxy dimethylphosphonate (**6**). The bicarbamyl radical (**15**) can lose carbethoxy radical to give ethyl diazacarboxylate (**16**), which then can pick up the carbethoxy radical (Figure 2) to give the hydrazyl radical (**17**). The latter can then abstract hydrogen to form 1,1-diethyl hydrazinecarboxylate (**7**).

Compounds **5** and **7** are isomers and have the same molecular weight, namely 176. However, the retention time of compound **7** is greater than that of compound **5**. This implies that compound **7** is more polar than compound **5**. The mass spectrum of compound **7** shows a peak at m/e = 59, which corresponds to $[H_2NN^+C_2H_5]$ moiety. There is another peak which corresponds to the loss of the NH_2 fragment. These considerations lend support to the suggested structure of compound **7**. The formation and the origin of both trimethylphosphate (**5**) and tetramethylpyrophosphate (**8**) already have been rationalized.[3,5] Figure 2 explains the formation of ethyl trimethylpyrophosphate (**9**). The ethyl methylphosphoryl radical formed from **6**, can add to the bicarbamyl radical (**15**) to give diethyl-N-[ethylmethylphosphonyl]-hydrazine dicarboxylate (**12**). The methyl radical formed in Figure 2, can abstract hydrogen from the methyl group of toluene to form the benzyl radical (**22**), which then adds to the bicarbamyl radical (**15**) to yield diethyl N-benzylhydrazinecarboxylate (**13**).

There are precedents for the addition of the phosphoryl radical to the carbon-carbon double bond.[18] The phosphoryl radical itself has been implicated in the formation of trimethylphosphtate.[19] And again, there are precedents for the splitting off the methyl radical from H-dimethylphosphonate (2) and trimethylphosphate (**5**).[20] Table I gives the mass spectral fragmentation of the compounds described in the narrative.

EXPERIMENTAL

All solvents were dry and freshly distilled prior to use. Mass spectra were obtained using a Finnigan TSQ-7000 GC/MS/MS equipped with a 30 m × 0.25 mm. i.d. DB-5 capillary column (J and W Scientific, Folsom, CA) or a Finnigan 5100 GC/MS equipped with a 15 m × 0.25 mm. i.d.Rtx-5 capillary column (Restek, Bellefonte, PA). The conditions on 5100 were: oven temperature 60–270°C at 10°C/min, injection temperature was 210°, interface temperature 230°C, electron energy 70 eV, emission current 500 μA and scan time 1 sec. The conditions on the TSQ-7000 were: oven temperature 60–270°C at 15°C/min, injection temperature 220°, interface temperature 250°C, source temperature 150°, electron energy 70 eV (EI) or 200 eV (CI) and emission current 400 μA (EI) or 300 μA (CI) and scan time 0.7 sec. Data was obtained in both the electron ionization mode (range 45–450 da) and chemical ionization mode (mass range 60–450 da). Ultrahigh purity methane was used as the CI agent gas with a source pressure of 0.5 Torr (5100) or 4 Torr (TSQ-7100). Routine GC analyses were accomplished with a Hewlett-Packard 5890A gas chromatograph equipped with a J and W Scientific 30 m × 0.53 mm i.d. DB-5 column (J and W Scientific, Folsom, CA).

Reaction of H-dimethylphosphonate (1) with Diethyl Azodicarboxylate (2)

A solution of a stoichiometric amount diethyl azodicarboxylate (**1**) in toluene (this was used as supplied by the Fluka Chemical Company) was added to stoichimetric amounts of H-dimethylphsophonate (**2**) and the whole was heated with atirring for 8 hr in an oil bath kept at 80∼90°C. After that, the reaction mixture was allowed to come to ambient temperature and was analyzed by GC. Since the reaction product was shown to be a highly complex mixture of compounds (**3**∼**14**), the solvent was removed under reduced pressure and the residue was subsequently analyzed and reanalyzed by GC-MS-EI. To confirm the molecular ion peaks and to determine the molecular weight of the unknown compound (**14**), the analysis was done in the GC-MS-CI mode also. The mass spectral fragmentation of the various compounds is given in Table I.

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